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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/886,044	06/30/97	BHATTACHARJEE A	7100/137

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EXAMINER
DEVI,S

ART UNIT	PAPER NUMBER
1541	

DATE MAILED: 09/14/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/886,044	Applicant(s) Bhattacharjee et al.
	Examiner S. Devi	Group Art Unit 1641

☒ Responsive to communication(s) filed on *Jun 19, 1998* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3, 5-8, and 15-17* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3, 5-8, and 15-17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Acknowledgment is made of Applicants' amendment filed 19 June 1998 along with Dr. Opal's declaration (paper no. 22). Claims 1-3, 5-9 and 11-18 are pending in this application, claims 9, 11 and 18 have been cancelled, claims 1, 2, 7, 12 and 16 have been amended. It is noted that Applicants have explicitly stated that claim 11 is cancelled. An action is issued on claims 1-3, 5-8 and 12-17.

2. Applicants' arguments with regard to rejoining claims 11-14 drawn to a process of using the vaccine have been fully considered. In light of the *Official Gazette* of 26 March 1996, rejoinder of these claims with the elected claims will be considered at the time of allowance depending on the status and scope of the claims at that time.

3. Rejection of claim 1 under 35 USC 112, first paragraph made because of the new matter is withdrawn in view of Applicants' amendment to the claim.

4. Rejection of claims 1-3, 5, 15-17 under 35 USC 112, first paragraph, is withdrawn in view of Applicants' amendments to the claims.

5. Rejection of claims 1-3, 5-9 and 15-17 under 35 USC 112, first paragraph, as failing to enable one skilled in the art to make and/or use the invention, is withdrawn in view of Applicants' arguments and Dr. Opal's declaration.

6. Rejection of claims 1-3, 5-9 and 15-17 under 35 U.S.C. § 103(a) as being unpatentable over Zollinger *et al.* is withdrawn. However, a new rejection of claims 1-3, 5-9 and 15-17 has been made below by the Examiner of record.

Claims Rejections - 35 USC §103

7. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are

applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

8. Claims 1-3, 5-9 and 15-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zollinger *et al.* (US 4,707,543) in view of Ziegler *et al.* (*New Eng. J. Med.* 307(20): 1225-1230, 1982) or Myers *et al.* (US 4,912,094) and Munford *et al.* (US 4,929,604).

Zollinger *et al.* teach the use of detoxified LPS obtained from *Escherichia coli*, non-covalently complexed with OMP of group B *Neisseria meningitidis* as a vaccine against infection. It is taught that the term polysaccharide includes lipopolysaccharide and capsular polysaccharide (column 2, lines 25-29). It is further taught that the process of the invention is "applicable to the preparation of detoxified lipopolysaccharide-outer membrane protein and capsular polysaccharide-outer membrane protein complexes wherein the lipopolysaccharide is noncovalently bonded the protein to form a complex" (column 4, lines 15-22). The process is further applicable to the preparation of such complexes derived from gram negative bacteria including *Escherichia coli* (column 4, lines 23-29).

Zollinger *et al.* do not specifically teach the J5 *Escherichia coli* polysaccharide complexed with meningococcal outer membrane protein.

Ziegler *et al.* teach a purified LPS of *E. coli* J5 and its role as an effective immunogen. Ziegler *et al.* teach that the "LPS of *E. coli* J5 lacks oligosaccharide side chains and that its core which is exposed is "nearly identical to that of most other gram-negative bacteria" (see the abstract). The J5 LPS-induced antibodies "conferred protection against Shwartzman reactions caused by purified endotoxins from bacterial species as widely varied as *E. coli*, *Salmonella typhimurium*, and the meningococcus", i.e. heterologous gram negative bacteria recited in claim 1 (see page 1226). Zeigler *et al.* describe the advantage of using *E. coli* J5 over that of its parent strain by

stating that in case of LPS obtained from the parent *E. coli* strain, the "core determinants are concealed by side chains" (i.e. O-specific side chains). Zeigler *et al.* further teach the ineffectiveness of antiserum raised to the LPS of J5's parent *E. coli* (which has O-specific side chain attached to the core determinant) against gram negative bacterial infections and also the association between high titers of antibodies to LPS-core determinants and low rates of shock and death observed in animal models. It is taught that this protection is independent of antibody to the O-specific side chain of LPS (see page 1226). Thus, Zeigler *et al.* clearly provide the motivation for one skilled in the art to use preferably *E. coli* J5 LPS that is devoid of O-specific side chain over it's parent *E. coli* strain that has O-specific side chain intact as an immunogen to treat sepsis caused by multiple gram negative bacterial pathogens.

Myers *et al.* teach that "the core region is highly conserved among LPSs obtained from different genera of *Enterobacteriaceae*" and that "immunity against the core region is ..... protective against a wide variety of Gram negative bacterial challenges" and "was demonstrated by the work of Ziegler *et al.*" (see column 2, lines 9-13). With reference to the use of LPS as a vaccine against gram-negative infections, Myers *et al.* explicitly teach that "LPS prepared from ..... from a strain that has a partially-complete (and therefore antigenically cross-reactive) core-region (e.g. ***E. coli* J5**)" can be used (emphasis added) (column 10, lines 4-9).

Munford *et al.* teach that "the structure of the lipid A moiety is highly conserved" in the LPS of many pathogenic bacteria including *Salmonella, Escherichia, Haemophilus* and *Neisseria*, and that LPSs may be used as vaccines to prevent gram negative bacterial sepsis by producing antibodies to R-core regions (see the abstract and column , lines 41-45). The structure of the R core region of LPS "is similar in most gram negative bacteria" (see column 1, lines 34-36).

It would have been obvious to one skilled in the art at the time the invention was made to substitute Zollinger's generic *Escherichia coli* LPS with its O-specific side chains intact, with Ziegler's or Myers' specific *E. coli* J5 LPS which is devoid of O-specific side chains, to produce the instant invention because, Zeigler *et al.* teach that O-specific side chains present in the LPS of parent *E. coli* strain "conceals" the protective core determinants whereas *E. coli* J5 LPS devoid of O-specific side chains has this protective core determinant exposed (and thus available for

recognition by the host immune system). One skilled in the art would be motivated to produce the instant invention for the expected benefit of using an immunogen that elicits protective response against multiple pathogenic bacterial species in addition to *E. coli* (for example *S. typhimurium* and the meningococcus) because of the exposed/unblocked conserved antigenic determinants that this immunogen presents to the host immune system as taught by Ziegler *et al.* or Myers *et al.* or Munford *et al.* One skilled in the art would have had a reasonable expectation of success in obtaining the vaccine of the instant invention since Ziegler's purified *E. coli* J5 LPS would be expected to function no differently than Zollinger's generic *E. coli* LPS when complexed with meningococcal outer membrane protein. Absent showing to the contrary claims 1-3, 5-8 and 15-17 are obvious over the prior art of record.

9. No claims are allowed.

10. Applicants amendment necessitated the new ground(s) of rejection presented in this Office Action.

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi whose telephone number is (703) 308-9347. The Examiner can normally be reached on Monday to Friday from 8.00 am to 4.00 pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

S. Devi, Ph.D.
3 September 1998

James C. Housel 9/9/98
JAMES C. HOUSEL
SUPERVISORY PATENT EXAMINER